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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte GEORG KALLMEYER, GERHARD WINTER,
CHRISTIAN KLESSEN, and HEINRICH WOOG

Appeal 2007-3118
Application 09/308,223
Technology Center 1600

Decided: May 28, 2008

Before, TONI R. SCHEINER, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

Claim 13 is representative.

13. A lyophilizate, comprising

- (a) a monoclonal antibody or a polyclonal antibody;
- (b) an amino sugar;
- (c) at least one amino acid; and

(d) a surfactant,
wherein the lyophilizate contains no poly ethylene glycols or additional proteins.

Cited References

| | | |
|-----------|---|--------------------------------|
| Andya | 6,267,958 B1 | March 1996 |
| Michaelis | 5,919,443 | July 6, 1999 |
| Metzner | US 6,204,036 ¹ or EP 0733,702 | Mar. 20, 2001 Feb. 10, 1996 |
| Kunihiro | EP 0689843 | June 22, 1995 |
| Osterberg | WO 94/07510 | April 14, 1994 |

Musetta A. Hanson et al., "Chapter 7, Introduction to Formulation of Protein Pharmaceuticals," *Stability of Protein Pharmaceuticals*, Plenum Press, NY (1992).

Manning et. al., "Stability of Protein Pharmaceuticals," *Pharmaceutical Research*, Vol. 6, No. 11, pp. 903-913 (1989)

Nema, "Freeze-Thaw Studies of a Model Protein, Lactate Dehydrogenase, in the Presence of Cryoprotectants," *J. Parent Sci. Technol.*, 47, p. 76-83 (1993).

Grounds of Rejection

Claims 13, 15-18 and 22-36 stand rejected under 35 U.S.C. § 103(a) as obvious over Andya in view of Michaelis.

¹ US 6,204,036 is an English equivalent of EP 0733,702.

DISCUSSION

Background

“The invention concerns lyophilized pharmaceutical preparations of monoclonal or polyclonal antibodies which contain a sugar or amino sugar, an amino acid and a surfactant as [a] stabilizer. In addition the invention concerns a process for the production of these stable lyophilizates as well as the use of a sugar or amino sugar, an amino acid and a surfactant as stabilizers of therapeutic or diagnostic agents containing antibodies.” (Spec. 1.)

Claims 13, 15-18 and 22-36 stand rejected under 35 U.S.C. § 103(a) as obvious over Andya in view of Michaelis. We select claim 13 as representative of the rejection before us since Appellants have not separately argued the claims. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner contends that

Andya [] teach a variety of lyophilizates comprising monoclonal or polyclonal antibodies, sugars, amino acids, and surfactants wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins; wherein the lyophilizate contains a single amino acid or two different amino acids; ... wherein the sugar comprises at least one member selected from the group consisting of a monosaccharide, a disaccharide and a trisaccharide (column 15 line 12); wherein the sugar comprises sucrose or trehalose; wherein the amino acid comprises histidine, glutamic acid; wherein the surfactant comprises a polysorbate (column 15)...

(Ans. 3.)

The Examiner acknowledges that Andya does not teach an amino sugar such as glucosamine, N-methylglucosamine, galactosamine, and neuraminic acid. (Ans. 3.) The Examiner relies on Michaelis for teaching “the advantages of an improved protein lyophilizate which contains amino sugars.” (Ans. 4.)

The Examiner concludes that:

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the lyophilizate of Andya *et al.* so as to include an amino sugar as taught by Michaelis *et al.* One would have been motivated to do so because Michaelis *et al.* make the surprising discovery that it is possible to produce stable forms of pharmaceutical agents when maltose, raffinose, sucrose, trehalose or amino sugars are used as additives (column 3, line 9). Michaelis *et al.* further teach that solid preparations which contain maltose, raffinose, sucrose, trehalose or amino sugars as auxiliary agents can be frozen or even stored at increased temperatures with no significant loss of protein quality. Hence, the teachings of Michaelis *et al.* suggest an improved and more versatile lyophilizate which can also contain amino sugar.

(*Id.* 4.)

On the other hand, Appellants contend that

[a]ntibodies and cytokines are in different protein classes and have different structures and therefore different stabilization requirements. Michaelis discloses the addition of an amino sugar to stabilize G-CSF protein not antibodies. Applicants respectfully point out that it is known that different protein classes required different stabilizers, not all stabilizers are suitable for all proteins.

(Br. 4-5.)

Andya teaches a stable lyophilized protein formulation. (Andya abstract.) Andya defines a protein to include proteins such as colony stimulating factors (CSFs) e.g., M-CSF, GM-CSF, and G-CSF (Andya, col. 7, ll. 8-10) as well as antibodies (Andya, col. 7, ll. 26-62). Thus Andya's disclosure relates to stable lyophilized proteins generally, including proteins which are antibodies. Michaelis also relates to stable lyophilized protein compositions, in particular a G-CSF protein, which include an amino sugar such as N-methyl glucose amine and galactosamine. (Michaelis, col. 11, Table 6.)

In making an obviousness determination over a combination of prior art references, it is important to identify a reason why persons of ordinary skill in the art would have attempted to make the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, (2007). When making such a determination, the scope of the prior art and level of ordinary skill must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

We find the cited evidence of record supports the Examiner's position that it would have been obvious to one of ordinary skill in the art to add an amino sugar to the stable lyophilized protein which may be an antibody or G-CSF described in Andya, as Michaelis similarly teaches stable lyophilized proteins, such as G-CSF, where amino sugars are used as stabilizing additives (Michaelis, col. 3, l. 9-12.)

In view of the above, we find the Examiner has identified a reason why persons of ordinary skill in the art would have attempted to make the claimed subject matter.

Appellants argue that it was not predictable that a formulation for stabilizing a cytokine would be successful with the antibody preparation of the present invention. (Br. 8.) Appellants put forth several publications as evidence of unpredictability in the art of protein stabilization in rebuttal to the Examiner's prima facie case of obviousness. These publications include Osterberg, Manning, Kunihiro, Hanson, Metzner and Nema which we will address in turn. We are not persuaded by Appellants' evidence and arguments.

Appellants argue that antibodies and cytokines are in different protein classes and have different structures and different stabilization requirements. (Br. 5.) However, Andya teaches that proteins, such as G-CSF, and antibodies may be lyophilized under similar conditions. (Andya, col. 6, l. 36 to col 7, l. 44.) In addition, Appellants' claims are directed generally to a lyophilizate of any antibody, encompassing both polyclonal and monoclonal antibodies, and the claims do not require any particular level of antibody stability. Thus, claim 13 reads on any antibody lyophilizate regardless of its stability.

In this vein, Osterberg and Manning are relied on by Appellants to teach "that different proteins are different in their physico-chemical properties" and that "protein stability encompasses many complicated and interrelated chemical and physical processes". (Br. 6.) However, as indicated herein, Appellants' claims are directed generally to a lyophilizate of a protein which is any antibody and require no specific degree of stability. Therefore, to support a prima facie case of obviousness, the Examiner need only provide a reason why one of ordinary skill in the art would include an

amino sugar in a protein lyophilizate, and that reason does not have to be the same as Appellants', i.e., to increase protein stability. The motivation to combine references does not have to be identical to patent owner's to establish obviousness. *In re Kemps*, 97 F.3d 1427, 1430, (Fed. Cir. 1996).

Appellants similarly rely on Kunihiro for the disclosure that a composition of thrombomodulin and albumin, purified gelatin, glycine, glucose or mannitol (Kunihiro 4: 4-7) fails to exhibit long term stability. Appellants argue that this teaching in Kunihiro contradicts that Michaelis' teachings can be applied to any and all pharmaceutical preparations.² (Br. 7.) Again, Appellants' claims are directed generally to any antibody lyophilizate and require no protein stability. In addition, the disclosure in Kunihiro relied on by Appellant does not establish that the thrombomodulin compositions listed possess no stability, only that the compositions possess no long term stability. Thus we are not persuaded by Appellants' argument.

Hanson discloses that certain amino acids did not stabilize *intravenous* immunoglobulin preparations (Br. 7). Hanson further describes that proteins in an aqueous phase must consider the influence of the solvent on protein conformation. (Hanson, p. 211.) Hanson indicates (Section 4.2.1

² However, we note that Preparation 10 (Kunihiro, p. 22) indicates that a composition of thrombomodulin protein, the amino acid - arginine and a surfactant resulted in a significant improvement in long term storage stability. Furthermore, Preparation 12, containing thrombomodulin, a sugar - maltose and a surfactant also resulted in a stable composition. (Kunihiro, p. 22.) These preparations of Kunihiro are in fact similar in composition to those of Michaelis, particularly formulation 11 (Michaelis, col. 6, Table 6) which discloses a stable composition comprising G-CSF, an amino sugar - galactosamine, an amino acid - phenylalanine, and a surfactant.

Lyophilization, p. 220 et. seq.) that lyophilization requires different protein stabilization considerations to address the effects of freezing. We have no evidence before us that *lyophilized* immunoglobulin preparations could not be prepared using the amino acids cited in Hanson and thus it is unclear how the intravenous composition disclosed in Hanson relates to the claimed lyophilized antibody. Again, the claims do not require a stabilized lyophilized composition.

Metzger (English equivalent, US 6,204,036) is relied on as showing that with Factor VIII, the amino acids histidine and glutamic acid exhibited stability during lyophilization without further additives. Appellants argue that this is in contrast to Michaelis' disclosure that "glutamic acid has no significant impact on storage stability." (Br. 7.) However, Michaelis does not disclose that glutamic acid cannot be used for lyophilization, only that it has no impact on storage stability. In particular, Michaelis teaches that glutamic acid can be added to lyophilized pharmaceutical preparations. (Michaelis, col. 5, ll. 27-32.) Therefore, we are not persuaded by Appellants' argument.

Finally, Nema is relied on by Appellants as evidence that a particular concentration of trehalose was an ineffective cryoprotectant for lactose dehydrogenase. (Nema, p. 81, col. 1, ll. 23-26.) The evidence in Table II of Nema (Nema, p. 70) indicates that trehalose is a better cryoprotectant and provides greater stability than mannitol. The claims require no particular degree of stability. Moreover there is no evidence before us that trehalose would not have been an effective cryoprotectant at higher concentrations. There is no evidence of the relevance of lactose dehydrogenase to the

claimed lyophilized antibody. In view of the above, we are not persuaded by Appellants' arguments.

After evidence or argument is submitted by the Appellants in response to an obviousness rejection, "patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). We find that a preponderance of the evidence supports the position of the examiner and the rejection is affirmed. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988).

SUMMARY

The obviousness rejection is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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